Appeal No. 2016-1619

United States Court of Appeals

for the

Federal Circuit

SUPERNUS PHARMACEUTICALS, INC.,

Plaintiff-Appellee,

– v. –

ACTAVIS INC., WATSON LABORATORIES, INC. - FLORIDA, nka Actavis Laboratories FL, Inc., ACTAVIS PHARMA, INC., WATSON LABORATORIES, INC., ANDA, INC.,

Defendants-Appellants.

APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY IN NO. 1:13-CV-04740-RMB-JS, JUDGE RENÉE MARIE BUMB

NON-CONFIDENTIAL BRIEF FOR PLAINTIFF-APPELLEE

July 8, 2016

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CERTIFICATE OF INTEREST

Counsel for plaintiff-appellee Supernus Pharmaceuticals, Inc. certifies the following:

1. Full name of party represented by me:	**2. Name of real party in interest represented by me (only include any real party in interest NOT identified in Question 3):**	**3. Parent corporations and publicly held companies that own 10% or more of stock in the party:**
Supernus Pharmaceuticals, Inc.	Supernus Pharmaceuticals, Inc.	None

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (and who have not or will not enter an appearance in this case) are:

Frommer Lawrence & Haug LLP - Sandra Kuzmich, Jason Lief, Laura Chubb, Stephanie Roberts (formerly with the firm)

Saul Ewing LLP - Sarah Sullivan

July 8, 2016

/s/ Nicholas F. Giove
Signature of counsel

Nicholas F. Giove
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CONFIDENTIAL MATERIAL OMITTED

The material redacted from this brief is subject to a Discovery-Confidentiality Order. The confidential information on pages 22-23 and 42 concern technical information about Actavis's Tablets that Actavis has designated confidential.

TABLE OF AUTHORITIES

Cases

Rules

Regulations

GLOSSARY

Supernus	Plaintiff-Appellee Supernus Pharmaceuticals, Inc.
Actavis	Collectively, Defendants-Appellants Actavis Inc., Actavis Laboratories FL, Inc., Actavis Pharma, Inc., Watson Laboratories, Inc., and Anda, Inc.
Br.	Actavis's Opening Appeal Brief
'898 patent	U.S. Patent No. 7,722,898
'131 patent	U.S. Patent No. 7,910,131
Patents-in-Suit	Collectively, the '898 and '131 patents
FDA	Food and Drug Administration
ANDA	Abbreviated New Drug Application
Actavis's ANDA	Actavis's ANDA No. 205444
Actavis's Tablets	Actavis's proposed generic Oxcarbazepine Extended-Release Tablets, 150, 300, and 600 mg, that are the subject of Actavis's ANDA
PVP-K90	Povidone, USP (Kollidon® 90 F)
SLS	sodium lauryl sulfate

STATEMENT OF RELATED CASES

Under Federal Circuit Rules 28(a)(4) and 47.5, Supernus states that no other appeal in or from the civil action *Supernus Pharmaceuticals, Inc. v. Actavis Inc.*, *et al.*, Civil Action No. 13-4740 (RMB/JS) (D.N.J.), the case from which the present appeal lies, was previously before this or any other appellate court. Supernus further states that the Patents-in-Suit have been asserted in *Supernus Pharmaceuticals, Inc. v. TWi Pharm.*, Civil Action No. 15-369 (RMB/JS) (D.N.J).

STATEMENT OF THE ISSUES

1. The claims require a "homogeneous matrix" comprising elements 1(a)-(d). The district court adopted, in relevant part, Actavis's proposed construction of the "homogeneous matrix" limitation: "a matrix in which the ingredients or constituents are uniformly dispersed." The district court found that Actavis's Tablets contain a matrix in which the ingredients are uniformly dispersed based on extensive fact and expert testimony regarding: (i) Actavis's manufacturing process; (ii) FDA uniformity testing; and (iii) confirmatory chemical imaging of Actavis's Tablets. Was it clear error for the district court to find that Actavis's Tablets contain a "homogeneous matrix"?

2. Element 1(c) of the claims requires an "agent that enhances the solubility" of the drug oxcarbazepine. The district court determined that PVP-K90—an ingredient in Actavis's Tablets—enhances the solubility of oxcarbazepine based on: (i) unrebutted testing conducted by Supernus's expert; (ii) literature from the manufacturer of PVP-K90 describing it as a "solubilizing agent;" and (iii) statements in the intrinsic record describing PVP as an agent that enhances the solubility

of oxcarbazepine. Was it clear error for the district court to find that PVP-K90 enhances the solubility of oxcarbazepine as required by claim element 1(c)?

3. To succeed, Actavis's written-description defense requires clear and convincing evidence that the patent specifications failed to convey to those skilled in the art that Supernus's inventors possessed the claimed "homogeneous matrix" formulations. The as-filed applications describe the composition, manufacturing process, and testing of multiple embodiments of the claimed "homogeneous matrix" formulations actually prepared by the inventors. Was it clear error for the district court to find adequate written-description support for the "homogeneous matrix" limitation?

4. To succeed, Actavis's indefiniteness defense requires clear and convincing evidence that the Patents-in-Suit fail to delineate the scope of the "homogeneous matrix" limitation with reasonable certainty. Fact and expert testimony confirmed that a skilled artisan would assess homogeneity based on the manufacturing process, standard FDA uniformity testing, and/or chemical imaging. Did the district court err in finding the "homogeneous matrix" limitation definite?

STATEMENT OF THE CASE AND SUMMARY OF THE ARGUMENT

Following a *Markman* hearing, summary-judgment proceedings, and a seven-day bench trial, Judge Renée Marie Bumb of the District of New Jersey issued a 136-page opinion finding that Actavis's Tablets infringe the Patents-in-Suit and that the patents are not invalid. Actavis appeals from two of the district court's infringement findings and the district court's rejection of its written description and indefiniteness defenses.

All four issues turn on purely factual disputes, reviewed by this Court for clear error. Actavis has failed to demonstrate any clear error in the district court's opinion, which was rendered after considering voluminous documentary evidence and weighing the testimony and credibility of eight fact witnesses and twelve experts.

I. Actavis's Tablets Contain a "homogeneous matrix"

The claims of Supernus's Patents-in-Suit require a pharmaceutical formulation wherein four ingredients (elements 1(a) – 1(d)) are contained in a homogeneous matrix. (*See, e.g.*, Appx240-41, claim 1). The district court adopted, in relevant part, Actavis's proposed

construction of "homogeneous matrix" and, using that definition, found that Actavis designed and achieved homogeneous matrix tablets.

The district court did not err in reaching this purely factual conclusion. The testimony of Actavis's own experts and employees; the manufacturing process used by Actavis; uniformity testing submitted by Actavis to the FDA; and confirmatory chemical images prove that Actavis's Tablets are homogeneous.

II. Actavis's Tablets Contain "at least one agent that enhances the solubility of oxcarbazepine"

The claims of Supernus's Patents-in-Suit also require an "agent that enhances the solubility of oxcarbazepine." (*See, e.g.*, Appx240-41, claim 1). The district court ruled that this straightforward phrase requires no construction; its plain meaning suffices. The district court found that one of the ingredients in Actavis's Tablets, PVP-K90, enhances the solubility of the active ingredient, oxcarbazepine. Here again, the vast weight of the evidence proves well beyond the "more likely than not" standard that Actavis's Tablets contain a solubility enhancer.

The specifications and prosecution histories of the Patents-in-Suit, pharmaceutical treatises, manufacturer product literature, Dr. Chyall's

testing, Dr. Little's testimony, Actavis's manufacturing process, and Actavis's admissions to the FDA prove that PVP-K90 enhances the solubility of oxcarbazepine in Actavis's Tablets.

For example, BASF, the manufacturer of PVP-K90, advertises it as a "[d]issolution enhancer" and "solubilizing agent." (Appx64; Appx12563-64 at 649:6-650:20; Appx8616; Appx8636). Supernus's expert, Dr. Chyall, tested the solubility of oxcarbazepine in solutions with and without PVP-K90 and proved that it enhances solubility. No Actavis witness criticized Dr. Chyall's test protocol or resulting data. Supernus's pharmaceutical formulation expert, Dr. Little, confirmed that Actavis manufactures its tablets by spraying PVP-K90 over the dry oxcarbazepine. This process assures that the PVP-K90 is co-located with oxcarbazepine—exactly where it needs to be to perform its solubilizing function.

III. The "homogeneous matrix" Claim Limitation Is Definite and Has Adequate Written-Description Support

The district court applied the proper legal standard for definiteness—requiring that the "patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art

about the scope of the invention with reasonable certainty." (Appx136-37).

Based on "persuasive[]"expert testimony, the district court found that "persons skilled in the art understood that 'homogeneous' means a mixture of two or more ingredients that are uniformly dispersed in a pharmaceutical formulation." (Appx137-38). Actavis's own experts and corporate representatives admitted that a homogeneous tablet may be distinguished from a non-homogeneous tablet by: (i) a review of the process by which the tablet is manufactured; (ii) standard FDA uniformity and dissolution testing; or (iii) chemical imaging. Actavis fails to cite any publication or expert opinion suggesting that a person of skill in the art would have difficulty understanding the scope of "homogeneous matrix" in the context of Supernus's Patents-in-Suit.

The district court also applied the proper legal standard for written description—requiring that the patent application "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." (Appx130). Based on express specification disclosures of several homogeneous matrix formulations—and methods for making and testing such formulations—

the district court correctly found that "as of the filing dates, Supernus was in possession of the claimed invention." (Appx131). The district court committed no clear error in reaching this purely factual conclusion.

ARGUMENT

I. The District Court Committed No Clear Error in Finding that Actavis's Tablets Satisfy the "homogeneous matrix" Limitation

The claims require a "homogeneous matrix" comprising elements 1(a)-(d). (*See, e.g.*, Appx240-41, claim 1). The district court adopted, in relevant part, **Actavis's** proposed construction—"a matrix in which the ingredients or constituents are uniformly dispersed" (Appx20)—and based on an extensive factual record determined that Actavis's Tablets comprise a "homogeneous matrix" as claimed. The district court committed no clear error in reaching this purely factual conclusion.

A. Actavis's Manufacturing Process Will Necessarily Result in Tablets that Have a "homogeneous matrix"

The district court correctly found that Actavis's Tablets exhibit the claimed uniform dispersion of matrix constituents based, in part, on Actavis's manufacturing process. (Appx35-40).

When the term "homogeneous" was added to claim 1 of the '898 patent during prosecution, the inventors stated that "one of ordinary skill in the art would appreciate that **the formulations derived according to the [manufacturing] protocol set forth in the Examples would necessarily comprise a homogen[e]ous matrix**." ((Appx14079-91 at Appx14089) (emphasis added); *see also* Appx13992-14003 at Appx13999-14001; Appx14053-61 at Appx14053, Appx14058; Appx14069-77 at Appx14072; Appx14079-91 at Appx14086, Appx14089-90; Appx2380 at 64:7-11)).

In other words, the inventors publicly acknowledged that—consistent with the understanding of those skilled in the art—the details of the disclosed manufacturing process alone are sufficient to assess homogeneity. The manufacturing process disclosed in Example 4 of the Patents-in-Suit is considered "high shear granulation." (Appx40; Appx239, col.10 ll.38-40; Appx285, col.10 ll.38-40). Actavis's Tablets are also manufactured by "high shear granulation." (Appx40).

Both parties agreed that "the **default objective** for a pharmaceutical formulator would be to create a homogeneous matrix." (Appx35-36 (citing Appx13406 at 1493:12-19)) (emphasis added). And the district court found that "[n]o evidence has been presented that indicates that the Actavis formulators sought to stray from this default objective." (Appx36).

Supernus's expert, Dr. Little, "testified at length regarding Actavis's manufacturing process." (Appx37). The district court recounted that testimony and concluded that "Actavis's manufacturing process establishes that its tablets comprise a homogeneous matrix." (Appx35-36).

Actavis's homogeneity expert, Dr. Muzzio, disagreed, arguing that Actavis's manufacturing process "results in 'relatively large granules'" and "uses gentler stirring." (Appx38 (citing Appx12843-44 at 929:23-930:9, Appx12881 at 967:12-19)). The district court correctly dismissed Dr. Muzzio's testimony because it contradicted admissions in Actavis's ANDA:

> Given Actavis's own description of the purpose of each step in its manufacturing process, the Court gives [Dr. Muzzio's] opinions little weight.

(Appx38).

Evidence of Actavis's thorough mixing, chopping, milling, and blending—coupled with the district court's finding that "Dr. Little persuasively testified that the homogeneity achieved in the blend by the previous steps is carried over to the compressed tablet" (Appx39)—amply support the district court's homogeneity finding.

Actavis argues that "[b]ecause the court misconstrued 'homogeneous matrix' as the result of conventional manufacturing processes, it erroneously elevated the method of manufacturing over direct evidence of structure." (Br. at 25). The district court did not, however, construe the term "homogeneous matrix" as resulting from any particular manufacturing process. Rather, it found that Actavis's manufacturing process (which tracks patent Example 4) supports a finding that the ingredients in Actavis's Tablets are uniformly dispersed. (Appx35-40).

While the claims are not product-by-process claims (Br. at 24-25), Actavis's manufacturing process is appropriate and persuasive evidence of its final tablet composition and structure. In *SmithKline Beecham Corp. v. Apotex Corp.*, under analogous circumstances, this Court found

infringement of a product claim requiring a particular crystalline form based on the fact that the accused tablets were manufactured by a process that necessarily generates the claimed crystalline form. 403 F.3d 1331, 1334, 1341 (Fed. Cir. 2005).

Actavis bases its manufacturing-process-related non-infringement arguments on: (i) the lack of SLS in Actavis's Tablets; and (ii) the use of intra-granular and extra-granular ingredients. (Br. at 34). Actavis was unable to sway the district court from finding that, regardless of the absence of SLS, Actavis's process produces uniform matrix tablets. (Appx38-39). As for the incorporation of intra-granular and extra-granular ingredients, the Patents-in-Suit state that the tablet ingredients "can be incorporated in the formulation either prior to or after granulation." (*See, e.g.*, Appx237, col.5 ll.1-5; *see also* col.5 ll.22-28; col.6 ll.25-26). Actavis's expert formulator, Dr. Hopfenberg, specifically admitted that "there can still be a resulting homogeneous matrix if some ingredients are added before granulation and some ingredients are added after granulation." (Appx13407 at 1494:5-9). The district court considered Actavis's "SLS" and "extra-granular-

ingredient" arguments, but properly "g[ave] these opinions little weight." (Appx38-39).

B. FDA Uniformity and Dissolution Testing Conducted By Actavis Quantitatively Proves that Its Tablets Have a Uniform Dispersion of Matrix Constituents

The district court found that the results of Actavis's blend uniformity, content uniformity, and dissolution testing "confirm that Actavis's manufacturing process results in a uniform dispersion of ingredients and establish that the Actavis Tablets comprise a homogeneous matrix." (Appx46). Actavis's own expert, Dr. Jacobs, testified that "there are a number of instrumental techniques to determine . . . what degree of homogeneity might be in [a] tablet," including testing of "the contents of the blender" (i.e., **blend uniformity**) and "tablet [] characteriz[ation]" (i.e., **content uniformity**). (Appx12345 at 431:9-12).[1] The district court found that "[t]hese tests, which the Actavis Tablets have indisputably passed,

[1] As per Fed. R. App. P. 28(e), Supernus notes that the parties dispute the admissibility of Dr. Jacobs's testimony. (Appx12334-40 at 420:21-426:3). The district court ultimately deemed it unnecessary to rely on this testimony and, therefore, declined to rule on its admissibility. (Appx39-40 n.12).

likewise demonstrate that the Actavis Tablets comprise a homogeneous matrix in which its constituents are uniformly dispersed." (Appx40).

1. Blend Uniformity

Blend uniformity "look[s] at the adequacy of the mixing" by confirming that samples from various locations within the blender contain the same amount of active ingredient (here, oxcarbazepine). (Appx41; Appx12541 at 627:5-8). Blend uniformity directly measures the amount of oxcarbazepine in each sample. But because the test is designed to assess the adequacy of mixing, the results serve as direct evidence of the uniformity of all ingredients. (Appx42-43).

The district court considered and specifically rejected Actavis's argument that blend uniformity does not show "how the ingredients are dispersed in finished tablets" (Br. at 32):

> Although blend uniformity tests examine only the blend, not the final tablet, the Court is persuaded by [Supernus's expert] Dr. Little's expert opinion that if the constituents are properly blended, the final product will necessarily be uniform.

(Appx42).

Significantly, Actavis's Director of Analytical Chemistry, Jack Chen, testified as Actavis's Rule 30(b)(6) designee for homogeneity testing that:

> [A] positive result or an in-specification result for blend uniformity would indicate that your **product** is homogeneous[.]

(Appx41; Appx12708 at 794:10-13).[2]

The district court further found that "Dr. Little persuasively testified that the homogeneity achieved in the blend by the previous steps is carried over to the compressed tablet." (Appx39). Actavis's Dr. Muzzio agreed, testifying that there is no evidence of "demixing" between blending and compression. (Appx12951 at 1037:5-9).

Dr. Muzzio also authored an article echoing his and Dr. Little's testimony:

> [T]he [homogeneity] of a pharmaceutical blend is usually determined by assessing the uniformity of the active ingredient distribution throughout the mixture **while the uniformity of the excipients is assumed**.

[2] Actavis's brief glaringly omits any mention of Jack Chen. And Actavis elected not to bring Jack Chen to trial, did not object to the question or his testimony at deposition, and did not seek to have him change or explain his testimony (via errata, redirect at deposition, or through live trial testimony).

(Appx12969-70 at 1055:24-1056:2; *see also* Appx8305) (emphasis added).

Reference texts such as the "Handbook of Pharmaceutical Granulation Technology" also confirm that the properties of the blend "largely dictate the **final product** properties." (Appx12965-67 at Appx12967 at 1053:7-8) (emphasis added).

The district court noted that "[i]t is undisputed that the Actavis ANDA product passed blend uniformity testing," thus proving that Actavis's Tablets comprise a uniform dispersion of matrix constituents. (Appx43).

2. Content Uniformity

Content uniformity assesses whether each finished tablet has the same amount of active ingredient (here, oxcarbazepine). (Appx43). The district court found that "[t]he Actavis Tablets passed content uniformity testing[,]" the results of which "are consistent with Actavis's manufacturing process and confirm that the Actavis Tablets comprise a homogeneous matrix." (Appx44).

Here again, Actavis asks this Court to ignore all content-uniformity evidence because "it does not test for excipients, and 'uniformity' requires only the same amount of drug in each tablet, not

whether all ingredients are uniformly dispersed within a tablet." (Br. at 32).

The district court credited Dr. Little's testimony rejecting this argument:

> Dr. Little explained that in measuring the active ingredient in each tablet, content uniformity testing also necessarily measures the quality of mixing in, as well as the homogeneity and uniformity of the final tablet. As with blend uniformity testing, the uniform dispersion of the excipients is assumed once the uniformity of the active ingredient is established.

(Appx43-44). The district court further found that "Dr. Little cogently explained that if the excipients were not uniformly dispersed, there would be localization of all constituents, including the active ingredient." (Appx44). Accordingly, passing content-uniformity testing "establishes that there is no localization of the active ingredient and, therefore, also no localization of the excipients." (Appx44).

The FDA's current good-manufacturing practices for finished pharmaceuticals (at 21 CFR § 211.110) also undercut Actavis's argument. 21 CFR § 211.110 requires companies to implement certain controls—including uniformity testing—to "assure batch uniformity and integrity of **drug products**." (Appx12539-40 at 626:5-6) (emphasis

added). The FDA's related guidance titled "Powder Blends and Finished Dosage Units—Stratified In-Process Dosage Unit Sampling and Assessment" likewise is "intended to assist manufacturers of human drug products in meeting the requirements of 21 CFR § 211.110 for demonstrating the adequacy of mixing **to ensure uniformity of** in-process powder blends **and finished dosage units**." (Appx12363 at 449:20-24; Appx23174) (emphasis added). And Actavis's Dr. Muzzio himself published an article that unambiguously states that "in-process dosage unit analysis," such as blend and content uniformity testing, is "**an accurate and reflective measure of homogeneity of [a] product**." (Appx44 at n.14; Appx12963-65 at 1049:17-1051:6).

Actavis relies on a district-court opinion, *Takeda Pharmaceuticals Co. v. Teva Pharmaceuticals USA, Inc.*, 542 F. Supp. 2d 342 (D. Del. 2008), for the proposition that inferring infringement from compliance testing is clear error. (Br. at 33). The accused products in *Takeda*, however, were manufactured by a specific "dispersion layering" process, with different ingredients intentionally localized in different layers (the antithesis of a uniform distribution). *Takeda*, 542 F. Supp. 2d at 350, 352. The *Takeda* court rejected the patentee's **contradictory** content-

uniformity evidence "in view of the fact that [the accused] product granules [we]re indisputably prepared by a series of dispersions rather than the premixing of components." *Id.* at 353.

Here, by contrast, the district court found that Actavis pre-mixes its ingredients with "highly efficient mixing," and then chops, blends, mills, and compresses the ingredients into uniform matrix tablets. (Appx37-38). Unlike *Takeda*, Actavis's manufacturing process, uniformity testing, and chemical imaging all **consistently** prove that Actavis's Tablets contain a homogeneous matrix.

3. *In Vitro* Dissolution Testing

The district court also credited the testimony of Supernus expert Dr. Little and inventor Dr. Kidane in finding that *in vitro* dissolution testing submitted by Actavis to the FDA "functions essentially as a proxy for tablet homogeneity by demonstrating that the tablets perform consistently with each other." (Appx46; see also Appx45). Quoting Dr. Little, the district court found that, "[i]f there's heterogeneities [sic] in the system, you would imagine that something would fall apart odd or funny, so you would get a different release profile." (Appx45).

The district court also credited inventor Dr. Kidane's testimony that "[i]f there is inhomogeneity there would be variability in the dissolution profiles." (Appx45).

Actavis does not dispute the district court's finding that "[t]he results of Actavis's dissolution tests show low variability between tablets," and thus cannot show clear error in the district court's conclusion that Actavis's dissolution tests further demonstrate homogeneity. (Appx45).

Actavis argues that the district court "improperly conflat[ed] 'homogeneous matrix'" and "the standards used for FDA approval of commercial products." (Br. at 14). It did not. This Court has held that "a district court may rely on an industry standard in analyzing infringement." *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1327-28 (Fed. Cir. 2010).

Actavis also argues that the district court "erred when it inferred infringement from compliance with regulatory standards in the face of direct evidence (the Raman imaging) that the ingredients in the Actavis tablets were not uniformly dispersed." (Br. at 33). *First*, the district court found that the FDA uniformity testing was **direct** evidence of

homogeneity. (Appx46). *Second*, even if the FDA uniformity testing did constitute circumstantial evidence of homogeneity, Supernus may "prove infringement by any method of analysis that is probative of the fact of infringement." *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1372 (Fed. Cir. 2009). "Circumstantial evidence is not only sufficient, but may also be more certain, satisfying and persuasive than direct evidence." *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1219 (Fed. Cir. 2006) (quoting *Michalic v. Cleveland Tankers, Inc.*, 364 U.S. 325, 330 (1960)).

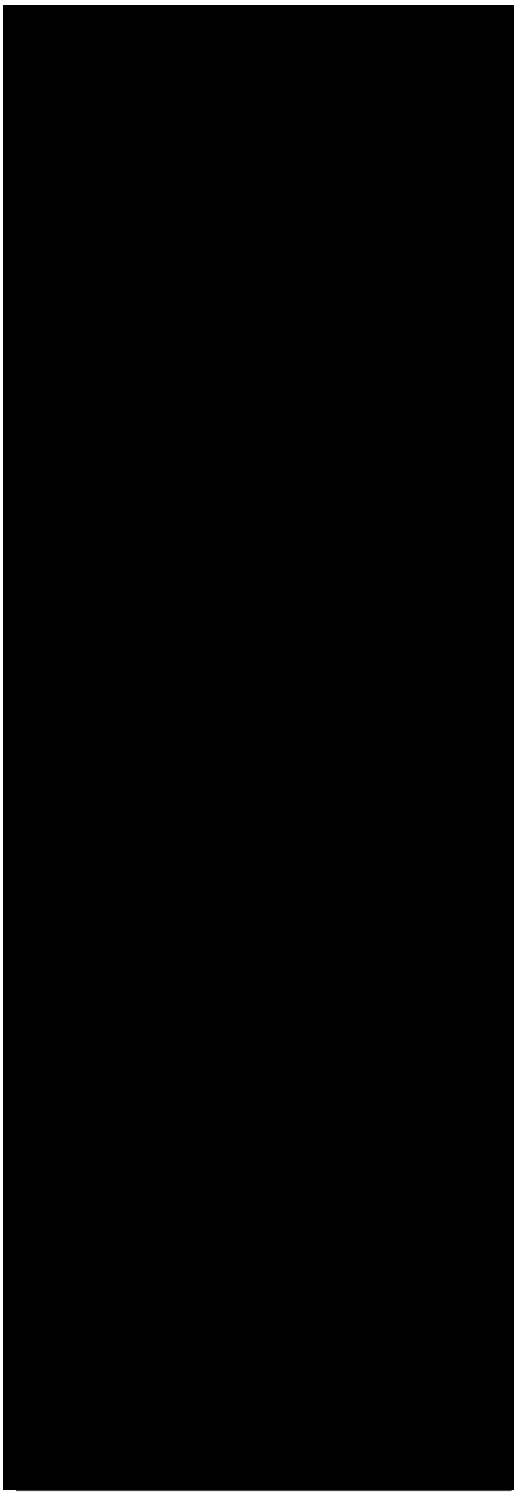
C. Chemical Images of Actavis's Tablets Confirm the District Court's Homogeneity Findings

The district court found that chemical imaging performed by Supernus's Dr. Bugay "confirms that both [Actavis's Tablets and Supernus's Oxtellar XR®] comprise a homogeneous matrix." (Appx60). The record below contains ample evidence supporting this factual determination.

Supernus's Dr. Bugay generated chemical images of the individual ingredients in Actavis's Tablets and determined that "[t]he constituents are not localized in one area alone, but rather are found throughout the tablet surface." (Appx51).

Actavis's homogeneity expert, Dr. Muzzio, also generated chemical images of Actavis's Tablets. The district court carefully considered Dr. Bugay's and Dr. Muzzio's imaging and corresponding analysis, and found Dr. Bugay's analysis more credible because, while "Dr. Muzzio only examined 7-8% of the tablet surface," Dr. Bugay's "procedure was repeated for 35,000 data points on each tablet, covering roughly 70% of the tablet's surface." (Appx47-48).

Dr. Bugay's images (reproduced below) confirm that Actavis's manufacturing process adequately mixed all ingredients to ensure "that each of the constituents in the Actavis ANDA product is uniformly dispersed throughout the tablet and, therefore, that each tablet comprises a homogeneous matrix" (Appx51):



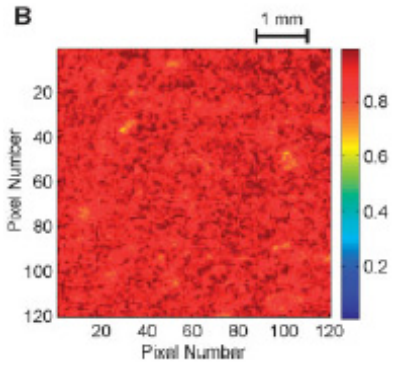
(Appx50; *see also* Appx23218-36, 23241-58).

The district court also considered Dr. Muzzio's images of the left and right half of Actavis's Tablets, and was particularly persuaded by Dr. Muzzio's concession "that 'the two halves don't look very different from each other,'" confirming that "there is no localization of constituents in the Actavis Tablets":

(Appx59 (citing Appx12827 at 913:23-24)).

The district court appropriately rejected Actavis's comparison of its tablets to Supernus's Oxtellar XR® and out-of-context chemical images pulled from the literature. (Br. at 28-31). *First*, the district court noted that Actavis's Tablets must be compared to "the claims of the relevant patents," not to a commercial embodiment (Oxtellar XR®) or to pictures found in the literature. (Appx55; Appx56-57 (citing *Zenith Labs., Inc. v. Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1423 (Fed. Cir. 1994)). *Second*, the comparators that Actavis urges this Court to

consider are taken completely out of context. For example, Actavis argues that, unlike its accused tablets, the image below shows "an even distribution of ingredient**s**" (Br. at 28-30) (emphasis added):



This image, however, depicts **a tablet made by compressing a single ingredient (acetaminophen)**. (Appx25921). This would have been apparent if Actavis had not misleadingly omitted from its brief the image's caption (highlighted below):

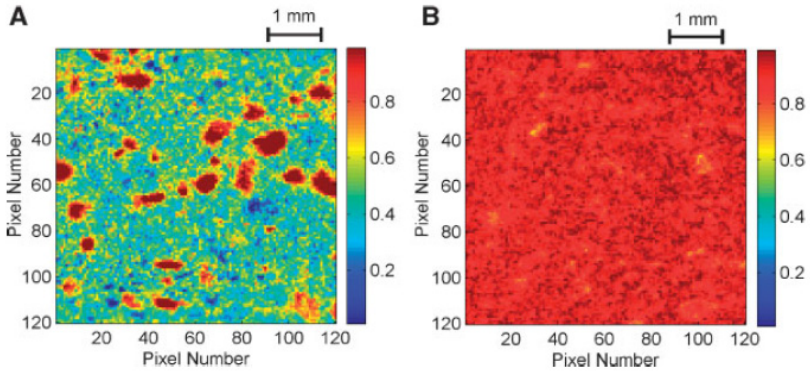
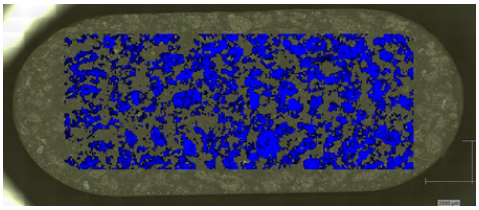


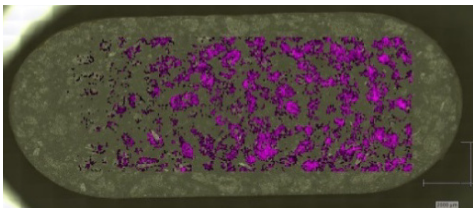
Figure 3. API concentration image of (A) nitrofurantoin capsule core and (B) pure acetaminophen compact. Length of scale bar in (A) and (B) is 1 mm.

(Appx25921). The uniform appearance of a single-ingredient tablet has no bearing on whether the multiple ingredients in Actavis's Tablets are

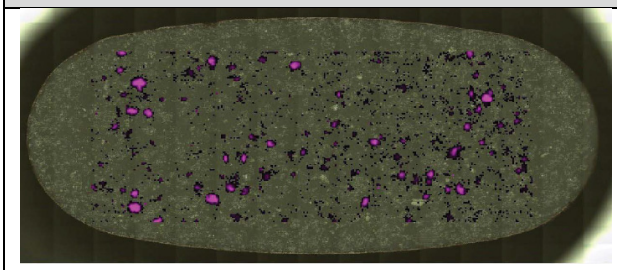
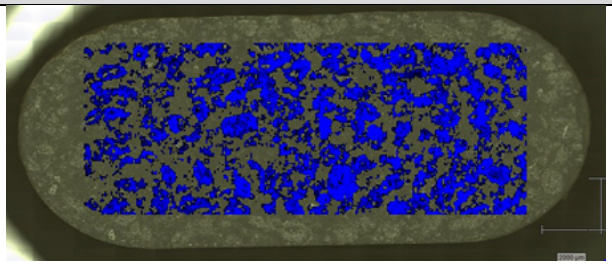
uniformly dispersed. Given the potential for misinterpreting out-of-context images, "the [District] Court, like [Actavis's] Dr. Muzzio, 'hesitate[s] to put too much emphasis just on pictures,' and does not." (Appx60 n.20 (citing Appx12957 at 1043:1-2)).

The district court also identified a fundamental inconsistency in Actavis's chemical-imaging analysis—an inconsistency that Actavis carries through to this appeal. Actavis argues that the images below of the oxcarbazepine and HPMC in its tablets "reveal[] non-uniformity." (Br. at 27):





The district court recognized, however, that Actavis's argument contradicts its analysis of other chemical-imaging evidence. For example, Actavis and its expert Dr. Muzzio repeatedly admit that the SLS image in the left panel of the table below is "very homogeneous," yet maintain that the oxcarbazepine image in the right panel is not homogeneous. (*Compare* Appx12907-08 at 993:10-994:2, *with* Appx12814 at 900:1-19).

SLS (Oxtellar XR®)	Oxcarbazepine (Actavis's Tablets)
	
(Actavis's Dr. Muzzio: "very homogeneous")[3]	**(According to Dr. Muzzio, Not Homogeneous)[4]**

Such demonstrably inconsistent analyses convinced the district court to credit Supernus's interpretation of the chemical-imaging evidence over Actavis's and Dr. Muzzio's. (Appx58-59).

The district court did not clearly err in finding that these three sets of chemical images confirm that "the Actavis Tablets comprise a homogeneous matrix, as construed by [the District] Court and as understood by a person of ordinary skill in the art." (Appx60-61). The district court carefully weighed the testimony of both parties' homogeneity experts and found Supernus's Dr. Bugay's analysis "more accurate[]." (Appx48). Actavis offers no basis for overturning the district court's credibility determination. Indeed, this Court has recognized that "[c]redibility determinations by the trial judge can

[3] Appx23252; Appx12907-08 at 993:10-994:2.

[4] Appx23219; Appx12814 at 900:1-19.

virtually never be clear error." *Celsis in Vitro, Inc. v. CellzDirect, Inc.*, 664 F.3d 922, 929 (Fed. Cir. 2012) (quotation marks omitted).

D. No Claim-Construction Issues Exist for This Court to Address and a New Trial is Not Warranted

Actavis devotes significant attention to arguing that "claim construction errors" require reversing the judgment of infringement. (Br. at 14-25). Actavis is judicially estopped from making this argument because the district court actually adopted, in relevant part, **Actavis's** proposed construction of "homogeneous matrix." *Cf. Schindler Elevator Corp. v. Otis Elevator Co.*, 593 F.3d 1275, 1282 n.1 (Fed. Cir. 2010) (refusing to entertain a patentee's assignment of error in a claim construction proposed by the patentee itself). Actavis even admits that "the district court[] . . . correctly construed 'homogeneous matrix.'" (Br. at 16).

During *Markman* proceedings, Supernus advocated for the addition of the clarifying phrase "substantially," as in a "substantially uniform" dispersion of ingredients. (Appx21-22). Actavis urged the district court to construe "homogeneous matrix" to mean a "matrix in which the ingredients have a uniform distribution." (Appx21). The district court ultimately ruled that "a 'homogeneous matrix' means 'a

matrix in which the ingredients or constituents are uniformly dispersed.'" (Appx27).

Actavis now confusingly asks this Court to readdress claim construction, arguing that "homogeneous matrix does not mean 'substantially' uniform." (Br. at 19). But the district court's opinion repeatedly states that "a 'homogeneous matrix' means 'a matrix in which the ingredients or constituents are uniformly dispersed.'" (Appx27). Applying that definition to the evidence presented at trial—Actavis's manufacturing process, FDA uniformity testing, and chemical imaging—the district court found as a matter of fact "that the Actavis Tablets comprise a homogeneous matrix, as construed by this Court and as understood by a person of ordinary skill in the art." (Appx60-61).

This Court should reject Actavis's attempt to relitigate the factual question of infringement on appeal under the guise of a claim-construction error. (*See* Br. at 25-35; *see also Tessera, Inc. v. ITC*, 646 F.3d 1357, 1364 (Fed. Cir. 2011). Actavis's "contention at best is a disagreement over the [district court's] ***application*** of [Actavis's] construction," a question of infringement that this court reviews for clear error. *Tessera*, 646. F.3d at 1364 (emphasis in original).

Actavis's request for a new trial similarly amounts to a thinly veiled disagreement over the district court's factual infringement determination. Actavis argues that it suffered "substantial prejudice" because the district court re-construed "homogeneous matrix" at trial. (Br. at 21-22). The district court did no such thing. It adopted Actavis's definition and found that under that definition, Actavis's Tablets comprised a homogeneous matrix.

Actavis's cries of surprise and prejudice are particularly disingenuous in view of the fact that Actavis's counsel expressly acknowledged a year before trial that, with respect to the Court's application of "uniform," "[i]t's not hard to see where we're going in this case":

> THE COURT: It seems to me, Mr. Weiss, that the parties really dispute what the term "uniform" means. **It sounds like where we're going, even once I construe the term "homogeneous matrix" then the parties will quibble about what the word "uniform" means**. Am I right?
>
> ACTAVIS'S COUNSEL: That may be the case. But what I want to emphasize and I think why we're arguing also about "substantially" is there is no question that what Supernus has added, which is this modifier which doesn't appear in the claims, is intended to give them more wiggle

> room, greater scope, greater claim scope, and more of an ability to prove infringement. **It's not hard to see where we're going in this case.**

(Appx2462-2463 (emphasis added); *see also* Appx2441; Appx2457-59; Appx2466-67).

Even if the district court did elaborate on its claim construction at trial, Actavis was on notice at least since the *Markman* hearing that the trial would involve a determination of whether Actavis's Tablets are "uniform." Actavis's lack of preparation is not grounds for a new trial. *See Power Mosfet Techs., L.L.C. v. Siemens AG*, 378 F.3d 1396, 1410-14 (Fed. Cir. 2004) (declining to order a new trial where the parties were on notice, prior to trial, of claim-construction issues that had not yet been resolved, and rejecting the patentee's claim of unfair surprise).

II. The District Court Committed No Clear Error in Finding that Actavis's Tablets Satisfy Claim Element 1(c): "agent that enhances the solubility of oxcarbazepine"

Claim element 1(c) requires an "agent that enhances the solubility of oxcarbazepine." (Appx240, col.12 ll.60-61; Appx286, col.12 ll.59-60). After considering unrebutted solubility testing, voluminous documentary evidence, and extensive trial testimony from Supernus's fact and expert witnesses, the district court correctly found that the

PVP-K90 in Actavis's Tablets satisfies claim element 1(c). (Appx61-73). The district court committed no clear error in reaching this purely factual conclusion.

A. Dr. Chyall's Unrebutted Solubility Testing—Conducted as Taught in the Patent Specifications—Confirmed that PVP-K90 Enhances the Solubility of Oxcarbazepine

The district court found that "[t]he results of [Supernus expert] Dr. Chyall's HPLC tests indicate that as the concentration of Kollidon 90F increases, so does the solubility of oxcarbazepine," and ultimately concluded that "Dr. Chyall persuasively testified that Kollidon 90F [PVP-K90] is an agent that enhances the solubility of oxcarbazepine, as required in element 1(c) of Claim 1." (Appx63). Actavis points to no clear error in the district court's factual assessment of Dr. Chyall's test results.

Dr. Chyall tested the solubility of oxcarbazepine in solutions with and without PVP-K90 to prove that PVP-K90 enhances the solubility of oxcarbazepine. (Appx62-63). Dr. Chyall conducted his tests according to the protocol disclosed in patent Example 3. (Appx62-63; Appx12196-201 at 282:20-287:2); *see Union Carbide Chems. & Plastics Tech. Corp. v. Shell Oil Co.*, 425 F.3d 1366, 1375 (Fed. Cir. 2005), *overruled on other*

grounds by Cardiac Pacemakers, Inc. v. St. Jude Med., Inc., 576 F.3d 1348 (Fed. Cir. 2009) (en banc) (affirming infringement verdict because patentee's expert "applied a test expressly approved by the patent specification").

The district court credited Dr. Chyall's test protocol, results, and corresponding testimony that the solubility of oxcarbazepine:

(i) in a control solution (no PVP-K90) was 0.063 mg/mL;

(ii) in 1% PVP-K90 increased to 0.078 mg/mL (**a 24% increase**);

(iii) in 5% PVP-K90 increased to 0.160 mg/mL (**a 154% increase**); and

(iv) in 10% PVP-K90 increased to 0.832 mg/mL (**a 1,221% increase**).

(Appx62-63). Actavis's trial witnesses did not criticize Dr. Chyall's test protocol or the results thereof.

Actavis's counsel now argues that Dr. Chyall did not "rule out the possibility that the very small difference between 1% PVP-K90 and the control was within experimental error, which he did not determine." (Br. at 46). On the contrary, Dr. Chyall testified that there "could be up to ten percent variability" in "the dilution of the sample prior to HPLC."

(Appx12213 at 299:11-12). But neither Dr. Chyall nor any of Actavis's witnesses testified that ten percent dilution variability could account for the **24% to 1,221%** increase in solubility that Dr. Chyall observed. In fact, Actavis's witnesses did not criticize Dr. Chyall's solubility testing or conduct their own competing experiments.

Actavis also points to an internal Supernus development report prepared by inventor Dr. Kidane that describes the composition and dissolution profiles of dozens of early experimental formulations. (Br. at 41). In describing two experimental formulations that contained PVP-K90, the document states:

> The incorporation of Povidone K90, a high molecular weight polyvinyl pyrrolidone, resulted in slow release profiles. Povidone K90 is a strong binder. It also lacks the solubilizing capacity of Povidone K25 resulting in slow release profiles.

(Appx25851).

Actavis relies on this statement to support its argument that "PVP K90 is not a solubility enhancer." (Br. at 41). The passage above plainly does not support that proposition. Rather, the statement that PVP-K90 "lacks the solubilizing capacity of Povidone K25 resulting in slow release profiles," means just what it says—PVP-K90 may, in

certain formulations, exhibit a relatively lower solubilizing capacity **compared to Povidone K25**. The development report nowhere states that PVP-K90 does not enhance the solubility of oxcarbazepine.

B. Manufacturer Product Literature and Pharmaceutical Treatises Confirmed that the PVP-K90 in Actavis's Tablets Enhances the Solubility of Oxcarbazepine

The district court also found that product literature from BASF, the manufacturer of PVP-K90, specifically describes the ingredient as a "[d]issolution enhancer" and as a "solubilizing agent":

Complexing agent and Dissolution enhancer	Kollidon 12 PF		Soluble povidones can form hydrogen bonds with compounds with complementary structures for improved dissolution.
	Kollidon 17 PF		
	Kollidon 25	*	
	Kollidon 30	*	
	Kollidon 30 LP	*	
	Kollidon 90 F	*	

Function	Product name	Application
Matrices and components for matrix forming	Soluplus®	Solubilizing agent, dispersant, crystallization inhibitor, immediate release matrix
	Kollidon® VA 64 / VA 64 fine	
	Kollidon® 12 PF	
	Kollidon® 17 PF	
	Kollidon® 30	
	Kollidon® 90 F	

(Appx64; Appx12563-64 at 649:6-650:20; Appx8616; Appx8636) (emphasis added).

The district court also relied on The Handbook of Pharmaceutical Excipients (5th ed. 2006), which similarly states that "Povidone [PVP] is used as a **solubilizer** in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid

dosage forms." (Appx64-65; Appx12565-67 at 651:21-653:3) (emphasis added). Dr. Linda Felton, one of Actavis's retained experts in this matter, edits Remington-Essentials of Pharmaceutics, which also characterizes PVP as a "**solubility and dissolution enhancer[]**." (Appx12562-63 at 648:1-649:5; Appx7935; Appx7155-58). Actavis did not address Dr. Felton's admission here or before the district court.

Actavis does not dispute that PVP-K90 is a well-known solubility enhancer. Instead, it argues that Dr. Chyall's testing did not account for the "effects of the other excipients in the Actavis tablets on the solubility of oxcarbazepine or on the ability of PVP-K90 to enhance the solubility of oxcarbazepine."[5] (Br. at 47). Actavis speculates that two ingredients disclosed in patent Example 3 (HBCD and SLS) may affect the solubilizing capacity of either HBCD or SLS standing alone. (Br. at 47-48). Actavis's Tablets, however, do not contain HBCD or SLS. And

[5] Actavis also attempts to discredit Dr. Chyall's testing by arguing that he "failed to explain" why the value he reported for the solubility of oxcarbazepine in buffer "was not even close to that reported in the patents." (Br. at 48 n.7). *First*, Actavis never raised this issue at trial. *Second*, as Dr. Chyall explained during summary-judgment proceedings (Appx10381 at Appx10390-93), his reported control solubility value (0.0626 mg/mL) is consistent with Actavis testing (0.07 mg/mL) (Appx15062) and FDA publications (0.07 mg/mL) (Appx14854-919 at Appx14875).

no witness identified any **specific ingredient in Actavis's Tablets** that might even hypothetically detract from the demonstrated solubilizing capacity of PVP-K90.

Mere attorney argument speculating about hypothetical ingredient interactions cannot render the district court's findings clearly erroneous in view of the substantial evidence of PVP-K90's universally acknowledged solubilizing effects. *See Monsanto Co. v. Scruggs*, 459 F.3d 1328, 1335 (Fed. Cir. 2006) (rejecting speculation about possible flaws in the patentee's infringement testing when the accused infringer failed to proffer concrete evidence that the hypothetical flaws actually manifested in the patentee's test results). Actavis "merely present[ed] hypothetical situations to suggest that [Supernus's] test results *could* be flawed." *Id.* "Given the evidence in the record, hypotheses alone are insufficient" to render the district court's fact finding clearly erroneous. *Id.*

C. The PVP-K90 in Actavis's Tablets Is Co-Located with Oxcarbazepine—Precisely Where It Needs to Be Located to Perform Its Solubility-Enhancing Function

Actavis ignores substantial record evidence in arguing that Dr. Chyall's tests "did not address any effect of PVP-K90 on the solubility of

oxcarbazepine in the Actavis tablets." (Br. at 45). The district court explicitly credited Dr. Little's testimony, which "rel[ied] in part on Dr. Chyall's solubility testing," in reaching its conclusion that PVP-K90 functions "as an agent that enhances the solubility of oxcarbazepine **in the Actavis Tablets**." (Appx63; Appx67) (emphasis added).

In making its tablets, Actavis sprays PVP-K90 all over dry oxcarbazepine to form PVP-K90/oxcarbazepine granules. (Appx37; Appx14692; Appx14699). Supernus's Dr. Little confirmed that this intentional co-location of PVP-K90 with oxcarbazepine would lead him to "expect in the actual tablet itself that [PVP-K90] would enhance the solubility of oxcarbazepine." (Appx12565 at 651:15-20). In other words, Actavis's manufacturing process affirmatively places PVP-K90—a universally recognized solubility enhancer—in intimate contact with the oxcarbazepine in **Actavis's Tablets** to ensure that the PVP-K90 is located exactly where it needs to be to function as a claim element 1(c) solubilizer.

Actavis also attempts to disparage Dr. Chyall's experiments by calling them "test tube test[s]," suggesting that a solubility experiment in test tubes containing aqueous (water-based) solutions—rather than

in actual tablets—"doesn't tell the whole story." (Br. at 46-48). *First*, Actavis took the exact opposite position earlier in this case, repeatedly urging the district court to define "agent that enhances the solubility of oxcarbazepine" to mean "ingredient that increases the solubility of oxcarbazepine **in an aqueous medium**" (i.e., in a test tube containing an aqueous/water-based solution). (Appx471; Appx509; Appx534; Appx568-69). *Second*, Dr. Chyall's testing tracked the standard protocol disclosed in Example 3 of the Patents-in-Suit. (Appx12196-201 at 282:20-287:2). *Third*, in attempting to prove obviousness during trial, Actavis and its expert Dr. Hopfenberg urged the district court to accept that several prior-art references that did not disclose any solubility experiments—test tube or otherwise—nevertheless disclosed claim element 1(c) solubility enhancers. (Appx13329 at 1416:2-18; *see also* Appx25135 at col.3 ll.8-9).

The district court did not clearly err in finding Dr. Chyall's testing and Dr. Little's corresponding testimony credible and sufficient to prove that PVP-K90 enhances the solubility of oxcarbazepine in Actavis's Tablets.

D. Actavis Admitted to the FDA that Its Tablets Contain PVP-K90 as a Surface Active Agent, One Category of Solubility Enhancer

In response to FDA inquiries about the apparent absence of a solubilizer, Actavis identified PVP-K90 as the solubility-enhancing agent in its tablets. (Appx66 (citing Appx21473-74)). The district court found these admissions to the FDA particularly persuasive evidence of the solubility-enhancing capacity of PVP-K90 in Actavis's Tablets. (Appx65-67).

Claim element 1(c) requires "at least one agent that enhances the solubility of oxcarbazepine selected from the group consisting of **surface active agents** [and four other categories of solubility enhancers]." (Appx240 at 12:60-62; Appx286 at 12:59-61) (emphasis added). Supernus's branded Oxtellar XR® contains SLS—a well-known surface active agent—as a claim element 1(c) solubilizing agent. (Appx32). In reviewing Actavis's ANDA, the FDA noted that Actavis's Tablets do not contain SLS and asked Actavis to comment on the apparent lack of a solubility-enhancing agent:

> 5. Oxcarbazepine has poor aqueous solubility, which is not pH dependent. As per the label for the referenced listed drug (RLD), OXTELLAR XR™ contains sodium lauryl sulfate as a wetting agent which according to literature is known to enhance the solubility of drugs. There is no solubility enhancing agent in the proposed generic formulation. Please comment how it would affect the performance of the drug product.

(Appx65-67; Appx21679).

In response to the FDA's inquiry, Actavis identified **PVP-K90** as an excipient used to "**increase[] the wettability of oxcarbazepine by reducing the contact angle**":

> Oxcarbazepine is formulated with an aqueous wet granulation process using a water soluble binder. This granulation process increases the wettability of Oxcarbazepine by reducing the contact angle.

(Appx65-67; Appx21473-74).

When asked "[w]hat water soluble binder is being referenced in direct response to item No. 5," Actavis's Dr. Hopfenberg replied "[p]resumably the response is related to the PVP K90." (Appx66; Appx13396 at 1483:2-9). The district court ruled that "Dr. Harold Hopfenberg, Actavis's expert witness, testified and the Court agrees that this 'water soluble binder' must be a reference to Kollidon 90F

[PVP-K90] since that is the only 'binder' listed in the chart in Actavis's ANDA outlining the composition of its generic tablets." (Appx66).

Further, when asked whether "[i]ncreasing the wettability of an active ingredient by reducing contact angle is really the quintessential way a surface active agent works," Dr. Hopfenberg acknowledged that it is "one way." (Appx66; Appx13397 at 1484:13-16). Dr. Hopfenberg also admitted that surface active agents "can contribute to wetting." (Appx13384 at 1471:17).

To summarize, when asked by the FDA to "comment how" the lack of SLS "would affect the performance of" Actavis's Tablets, Actavis responded by identifying PVP-K90 as a wetting/solubility enhancing agent.

E. The Amount of PVP-K90 in Actavis's Tablets (0.5%) Is Sufficient to Enhance the Solubility of Oxcarbazepine

The district court found that PVP-K90 "acts as an agent that enhances the solubility of oxcarbazepine **in the Actavis Tablets**." (Appx67) (emphasis added). Actavis argues, without factual or legal basis, that "Supernus presented no evidence showing that the **trace amount** of PVP-K90 in the Actavis tablets does this," i.e., enhances the solubility of oxcarbazepine. (Br. at 44) (emphasis added). Actavis's

statement that PVP-K90 exists in only "trace amounts" in Actavis's Tablets is demonstrably false.

First, depending on dosage strength, Actavis stipulated that each of its tablets affirmatively includes [redacted] mg of PVP-K90 [redacted]:

[redacted]

(Appx33 (citing Appx22940)) (emphasis added). No witness testified that these quantities represent "trace amounts." In fact, the words "trace amounts" were never spoken at trial. By contrast, Actavis's ANDA explicitly states that its tablets contain "trace amounts" of Opacode black imprinting ink. (Appx33 (citing Appx22940)). Actavis's ANDA confirms that, unlike Opacode ink, the amount of PVP-K90 far

exceeds what Actavis or the FDA consider to be "trace amounts." (Appx33 (citing Appx22940)).

Second, Actavis admitted to the FDA that the PVP-K90 in its ANDA Tablets "increases the wettability of oxcarbazepine by reducing the contact angle," i.e., functions as a solubilizer/surface active agent. (Appx65-67; Appx21473-74). Thus, Actavis admitted to the FDA that PVP-K90 does not appear in mere "trace amounts," but rather exists in sufficient quantities to function as a solubilizer/surface active agent.

Third, as noted above, the district court found that, during manufacturing, Actavis sprays PVP-K90 all over dry oxcarbazepine to form PVP-K90/oxcarbazepine granules. (Appx37; Appx12565 at 651:15-20). Supernus's Dr. Little confirmed that the **co-location of 0.5% PVP-K90 with oxcarbazepine** ensures that "in the actual tablet itself [] it would enhance the solubility of oxcarbazepine." (Appx12565 at 651:19-20).

Fourth, prior art cited and discussed in the prosecution histories of the asserted patents identifies **0.5%** PVP—the same amount used in Actavis's Tablets—as a claim element 1(c) solubility enhancing agent. The district court noted that:

> [I]n addressing the prior art, the Patent Examiner identified another patent [the '452 patent] which disclosed a pharmaceutical formulation comprising several constituents, including polyvinyl pyrrolidone [PVP]. After polyvinylpyrrolidone [PVP], the patent examiner added a note in parentheses: "(a surface acting agent; at least one agent that enhances the solubility of oxcarbazepine; that polyvinylpyrrolidone is known in the art as a surface active agent, . . .).

(Appx64 (citing Appx14176)). The '452 patent cited by the patent examiner discloses PVP in the range of about **0.5%** to 5%, which the examiner characterized as an "agent that enhances the solubility of oxcarbazepine." (Appx64; Appx9905, col.4 ll.3-10; Appx14176).

Fifth, in a failed attempt to prove obviousness, Actavis repeatedly admitted during trial, and in its post-trial briefing, that prior-art references containing far less than 0.5% solubility enhancer satisfied claim element 1(c). For example, Actavis urged the district court to invalidate Supernus's patents based, in part, on an example in the "Rudnic" prior-art reference that included 0.5% of a surface active agent (one category of solubility enhancer). (Appx26053; *see* Appx13329 at 1416:2-18). Rudnic also discloses quantities of surface active agent that are an order of magnitude lower than the amount of PVP-K90 in

Actavis's Tablets (0.**5**% in Actavis's Tablets v. 0.**05**% in Rudnic). (Appx25135, col.3 ll.8-9). Although the district court rejected Actavis's obviousness arguments—a ruling that Actavis does not challenge—these admissions undercut Actavis's suggestion that 0.5% PVP-K90 is a non-functional or "trace amount" of solubility enhancer.

Finally, Actavis mischaracterizes Dr. Bugay's testimony in arguing that "the Raman images made by [Dr. Bugay] of the Actavis tablet could not even detect the PVP-K90 because of its trace amount." (Br. at 44). The district court correctly ruled that Dr. Bugay's testimony does not support that conclusion. (Appx53-54). Dr. Bugay used microtomy to expose an interior layer of Actavis's Tablet, and then generated chemical images of that layer to confirm homogeneity. Dr. Bugay never testified that chemical imaging could not detect 0.5% PVP-K90. On the contrary, he explained that:

> [W]ith respect to **the slice that we were working at**, I did not see any [PVP-K90]. So, either the Povidone was at too low of a concentration **on that slice** or nonexistent **on that slice**, as her Honor mentioned.

(Appx12273-74 at 359:25-360:3) (emphasis added). Dr. Bugay used a helpful "iceberg" analogy at trial to explain the absence of PVP-K90 on

the exposed tablet layer. In short, if the particles of PVP-K90 in Actavis's Tablets are visualized as individual icebergs dispersed throughout the tablet, then depending on where Dr. Bugay's random slice occurred, he may have cut through a particle at the tip of the iceberg (resulting image shows a low concentration of PVP-K90); in the middle of the iceberg (resulting image shows a larger concentration of PVP-K90); or he may have missed the iceberg all together (resulting image shows no PVP-K90). (Appx53-54; Appx12258 at 344:3-10; Appx12326 at 412:3-18). Dr. Bugay explained that PVP-K90 "happened not to be at a detectable level **on the slice that [he] examined**," but is necessarily present in Actavis's Tablets. (Appx12273-74 at 359:24-360:17). The district court found Dr. Bugay's "explanation credible and persuasive." (Appx54).

Dr. Chyall's testing, Dr. Little's analysis of the co-location of PVP-K90 and oxcarbazepine in Actavis's Tablets, Actavis's ANDA composition chart, Actavis's statements to the FDA, prior art cited during prosecution, and literature cited by Actavis during trial support the district court's factual determination that the amount of PVP-K90

used by Actavis (0.5%) enhances the solubility of oxcarbazepine in Actavis's Tablets.

F. The District Court's Infringement Analysis Properly Applied the Undisputed Plain Meaning of "agent that enhances the solubility of oxcarbazepine"

1. Actavis Waived Its Argument that Claim Element 1(c) Excludes PVP-K90

During claim-construction proceedings below, Actavis proposed that "agent that enhances the solubility of oxcarbazepine" be construed as "ingredient that increases the solubility of oxcarbazepine in an aqueous medium." (Appx471; Appx509; Appx534; Appx568-69). Actavis was on notice of Supernus's contention that PVP-K90 satisfies claim element 1(c) long before it proposed this claim construction. (*See* Appx391-96; Appx458-63 (providing for the disclosure of infringement contentions prior to claim-construction proceedings)). Yet Actavis never advocated for a construction that would—as it argues now (*see* Br. at 35-37, 39-40)—exclude PVP-K90 from the scope of the claims.

Actavis has waived any argument that claim element 1(c) should be construed to exclude PVP-K90 because it may not introduce new claim construction arguments on appeal or alter the scope of the claim-construction positions it took below. *Enovsys LLC v. Nextel Commc'ns,*

Inc., 614 F.3d 1333, 1344-45 (Fed. Cir. 2010) (finding waiver of a claim-construction argument not raised with the district court and rejecting the accused infringer's attempt to recast the argument as an infringement issue).

The district court ultimately determined that "agent that enhances the solubility of oxcarbazepine" requires no construction; its plain meaning suffices. (Appx2481 at 165:18-21). Actavis is nevertheless limited on appeal to the construction that it previously proposed. *See Digital-Vending Servs. Int'l, LLC v. Univ. of Phoenix, Inc.*, 672 F.3d 1270, 1273 (Fed. Cir. 2012) (finding new claim-construction argument waived even though the district court adopted neither party's proposed construction). Based on Actavis's originally proposed construction, PVP-K90 satisfies claim element 1(c) as long as it "increases the solubility of oxcarbazepine in an aqueous medium." The district court credited Dr. Chyall's testing proving that it does. (Appx62-63). That ruling may be overturned only upon a finding of clear error. *See Cadence Pharm. Inc. v. Exela PharmSci Inc.*, 780 F.3d 1364, 1368 (Fed. Cir. 2015).

2. The District Court Properly Construed "agent that enhances the solubility of oxcarbazepine" to Have Its Plain Meaning—an Agent that Enhances the Solubility of Oxcarbazepine in Actavis's Tablets

Actavis now—for the first time—urges this Court to construe claim element 1(c) to mean "an agent that functions to enhance the solubility of oxcarbazepine in the Actavis tablets." (Br. at 39) (emphasis in original). This definition—while different from the definition Actavis proposed during claim construction—is precisely the "plain meaning" definition applied by the district court to find infringement:

> [T]he Court concludes that Kollidon 90F acts as an agent that enhances the solubility of oxcarbazepine **in the Actavis Tablets**. The Actavis Tablets, therefore, comprise an element 1(c) solubility enhancing agent in the form of Kollidon 90F.

(Appx67) (emphasis added). The district court determined that: (i) PVP-K90 is an agent that enhances the solubility of oxcarbazepine; and (ii) PVP-K90 functions to enhance the solubility of oxcarbazepine **in Actavis's Tablets**. (Appx63; Appx67). These purely factual determinations do not implicate the district court's claim construction because, as Actavis acknowledges, "[t]here really is no dispute here regarding [claim element 1(c)'s] ordinary meaning." (Br. at 38).

Actavis does not properly allege any "legal" error in the district court's claim element 1(c) infringement analysis. In fact, Actavis admitted that no disclaimer occurred, and "**[t]he issue now is one of fact, i.e., whether the povidone K90 in the Actavis tablets satisfies element 1(c).**" (Appx26269) (emphasis added).

Actavis takes issue with the district court's findings of fact concerning: (i) excerpts from the patent specifications; (ii) inventor trial testimony; and (iii) correspondence between the FDA and Actavis. The district court carefully heard, analyzed and dismissed each of these factual arguments in concluding that Actavis's Tablets satisfy claim element 1(c). (Appx65-69).

3. The Specifications and Prosecution Histories of Supernus's Patents Expressly Disclose PVP as an Agent that Enhances the Solubility of Oxcarbazepine

The patent specifications and the prosecution history of the '898 patent confirm that PVP is a surface active agent that enhances the solubility of oxcarbazepine in Actavis's Tablets.

Actavis confusingly suggests that "[t]he patents rule out that PVP, and specifically PVP-K90, is an agent that enhances the solubility of oxcarbazepine in the formulation." (Br. at 39). On the contrary, as the

district court noted, the patent specifications expressly identify "low molecular weight polyvinylpyrrolidone [PVP]" as a "preferred" solubilizer. (Appx63; Appx237, col.5 ll.9-15; Appx283, col.5 ll.12-18). The district court further noted that nothing in the intrinsic record limits the claimed solubilizers to the preferred "low molecular weight" PVPs. (Appx70). Moreover, the district court credited Dr. Little's unrebutted testimony that "molecular weight [low or high] is not going to impact whether or not you are able to form a bond complex with the molecular structure of [povidone]" to increase solubility. (Appx63-64; Appx12559 at 645:15-17). The specifications can hardly be read to "rule out" PVP as a solubility enhancer in view of the disclosure specifically identifying "low molecular weight polyvinylpyrrolidone [PVP]" as a "preferred" solubilizer.

Relatedly, the district court acknowledged that, during prosecution of the Patents-in-Suit, the Patent Examiner expressly characterized PVP—not just low-molecular-weight PVP—as an "agent that enhances the solubility of oxcarbazepine." (Appx64; Appx14176).

a. Example 1 Does Not Disclaim or Disavow PVP-K90 as a Potential Claim Element 1(c) Solubility Enhancer

Actavis relies heavily on Example 1, Table 1 to argue that "PVP-K90 (the specific grade in the Actavis tablet), is not an agent that enhances the solubility of oxcarbazepine in the accused Actavis tablets." (Br. at 50). Specifically, Actavis states that:

> In describing the three non-enhanced oxcarbazepine formulations (one of which contains PVP-K90) of Example 1, Table 1, the patent specification states that "FIG. 1 shows the dissolution profiles for the three exemplary (CR-F, CR-M, and CR-S) oxcarbazepine formulations containing no **solubility/release enhancer**."

(Br. at 40).

Actavis's reading of the specifications ignores repeated, express teachings that "**[a] combination of solubility and release promoters is contemplated in this invention**." (Appx68-69; Appx236 col.4 ll.14-16, col.3 ll.56-60; *see also* Appx11989 at 75:11-23) (emphasis added). The specifications explain that this combination of ingredients is essential because the claim element 1(d) release promoters "dissolve[] rapidly," leaving pores, i.e., increased surface area for water to flow into the tablet and contact the poorly soluble oxcarbazepine. (Appx236 col.4 ll.22-27). "This increased surface area

enhances the efficiency of the [1(c)] solubilizer(s), and hence, the overall solubility and release rate of the drug is enhanced." (Appx236, col.4 ll.27-29).

Supernus inventor, Dr. Bhatt, confirmed at trial that a solubility enhancing agent, alone, is not sufficient to enhance solubility because "the tablets needed more porosity to allow the fluid, the media, to go into the tablet and dissolve or help dissolve the drug along with the [element 1(c)] solubility enhancer." (Appx68; Appx11989 at 75:14-17). Dr. Bhatt and his co-inventors "modif[ied] the formulation one more time by incorporating [an element 1(d)] pH-dependent polymer[,] [w]hich will dissolve at a particular pH, and when it dissolves, it leaves behind [an] empty cavity, that allows, then, the water or the media to come in and help dissolve the drug along with the [element 1(c)] solubility enhancer." (Appx11989 at 75:18-23). Dr. Bhatt's testimony that Actavis quotes—suggesting that the Table 1 formulations lack solubility enhancement (Br. at 40)—confirms that the Table 1 formulations lack the critical synergistic combination of a solubility enhancer (element 1(c)) and release promoter (element 1(d)) necessary to sufficiently solubilize oxcarbazepine.

The parties do not dispute that the "non-enhanced" formulations in Table 1 lack a claim element 1(d) release promoter. (Appx239, col.9 ll.11-33). Nor do they dispute that the "non-enhanced" CR-F and CR-S formulations lack a claim element 1(c) solubilizer. (*Id*.). Only one "non-enhanced" formulation in Table 1 (CR-M) contains the element 1(c) solubility enhancing agent Kollidon 90 [PVP-K90]. (*Id*.). Thus, the patents' characterization of the "non-enhanced" formulations of Table 1 as "containing no **solubility/release enhancer**" means just what it says—the formulations (CR-F, CR-M, and CR-S) lack either a 1(c) solubility enhancer, a 1(d) release promoter, or both. (Appx235, col.2 ll.60-62) (emphasis added). Actavis's attempt to interpret the statement "containing no solubility/release enhancer" to mean that the Table 1 "non-enhanced" formulations all lack a claim element 1(c) solubility enhancer ignores the plain language of the specifications.

After hearing the testimony of two inventors (including Dr. Bhatt) and both parties' experts, the district court concluded that it "does not agree with the Defendants' argument that the 'examples in the specification also directly support the conclusion that . . . PVP [is] not [a] solubility enhancer[]":

> The Supernus Patents clearly state that a "combination of solubility and release promoters is contemplated in this invention." Id. at col. 4, ll. 14-17. The description of Table 1 states that the non-enhanced formulations contain no "solubility/release enhancer," referring, in this Court's opinion, to the combination of solubility and release promoters required in the invention. This is confirmed by Dr. Bhatt's testimony that solubility enhancing agents alone were insufficient and that a release promoter was also required. Tr. 75:11-17 (Bhatt Direct) (". . . the tablets needed more porosity to allow the fluid, the media, to go into the tablet and dissolve or help dissolve the drug along with the solubility enhancer.").

(Appx67-68). Actavis has failed to demonstrate that the district court's interpretation of Table 1 (and Dr. Bhatt's testimony) was clearly erroneous.

b. Example 4 Does Not Disclaim or Disavow PVP-K90 as a Potential Claim Element 1(c) Solubility Enhancer

Actavis also relies on Example 4, Table 4 to argue that the patent specifications "rule out" PVP-K90 as an agent that enhances the solubility of oxcarbazepine. Specifically, Actavis states that:

> [B]oth the "enhanced" and "non-enhanced" formulations of Table 4 contain PVP. (Appx239-40 at 10:55-11:15). Thus, the PVP in the non-enhanced formulation (CR), described as "without solubility enhancer," cannot be an "agent that enhances the solubility of oxcarbazepine."

(Br. at 39-40).

The district court acknowledged that "Table 4 lists the composition of one enhanced and one non-enhanced oxcarbazepine formulation," and that the "non-enhanced formulation is described in the Supernus Patents as one 'without solubility enhancer.'" (Appx67). The district court nevertheless rejected Actavis's Table 4 disclaimer argument because, like the non-enhanced formulations in Table 1, "the non-enhanced formulation in Table 4 does not contain a combination of solubility enhancing and release promoting agents, while the enhanced formulation has both." (Appx68).

The district court further found that even if "the ["without solubility enhancer"] description of the non-enhanced formulation in Table 4 is not referring to the combination of solubility and release promoters, the Court still finds it irrelevant to its analysis of whether Kollidon 90F [PVP-K90] satisfies claim element 1(c) **as [PVP-K90] is not present in either of the formulations in Table 4**." (Appx68) (emphasis added).

To summarize, the ingredient at issue in this appeal is PVP-K90. The "enhanced" and "non-enhanced" formulations in Table 4 do not

include the ingredient PVP-K90. Thus, Table 4's disclosure cannot represent a clear disavowal of PVP-K90 as a claim element 1(c) solubility enhancer. *Retractable Techs., Inc. v. Becton, Dickinson & Co.*, 653 F.3d 1296, 1306 (Fed. Cir. 2011) ("To disavow claim scope, the specification must contain expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope.") (internal quotation marks omitted).

The district court summarized its carefully considered PVP-K90 infringement ruling as follows:

> Given the extensive expert testimony from Dr. Little and Dr. Chyall, Dr. Chyall's solubility testing, and the scientific literature available, the Court concludes that Kollidon 90F acts as an agent that enhances the solubility of oxcarbazepine **in the Actavis Tablets**. The Actavis Tablets, therefore, comprise an element 1(c) solubility enhancing agent in the form of Kollidon 90F.

(Appx67) (emphasis added). Actavis has identified no basis for disturbing this factual determination.

III. Written Description: Supernus's Inventors Possessed the Claimed "Homogeneous Matrix" Formulations When They Filed Their Patent Applications

The district court applied the proper legal standard for written description—requiring that the application "reasonably convey[] to

those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." (Appx130-31 (citing *Ariad Pharm., Inc. v. Eli Lilly*, 598 F.3d 1336, 1351 (Fed. Cir. 2010))). The district court correctly found—based on fact and expert testimony and express statements in the specifications and prosecution history—that "as of the filing dates, Supernus was in possession of the claimed invention." (Appx131). The district court committed no clear error in reaching this purely factual conclusion.

A. The District Court's Written-Description Finding Is Supported by Fact and Expert Testimony and the Patent Specifications and Prosecution Histories

The district court found that "Example 4 explicitly (not superficially) discloses the step by step manufacturing process used by the inventors to produce a homogeneous matrix tablet." (Appx131-32). Example 4 (disclosed in the as-filed application) not only sets forth each step **actually** followed by the inventors to make three different homogeneous matrix tablets, but also concludes with a disclosure of subsequent analytical testing conducted on those homogeneous tablets. (Appx239). Specifically, Example 4 discloses that the inventors "manufactured" homogeneous tablets by "high shear granulation,"

wherein the ingredients were "blended," "chopp[ed]," "placed in an oven to dry," "screened," and "tableted." (Appx239). The resulting tablets were tested for dissolution. (Appx239; *see also* Appx225-26).

The district court additionally relied on the following prosecution-history statement directly linking the manufacturing protocol of Example 4 to the homogeneous tablets actually made by the inventors:

> [O]ne of ordinary skill in the art would appreciate that the formulations derived according to the [manufacturing] protocol set forth in the Examples would necessarily comprise a homogeneous matrix.

(Appx40 (citing Appx14089)). The district court found that this statement from Example 4 constitutes "'descriptive matter' that goes beyond simply describing the prior art as Actavis argues." (Appx134).

The district court further credited expert testimony from Supernus's Dr. Little confirming the link between the manufacturing process of Example 4 and the production of formulations having a homogeneous matrix. (Appx132 (citing Appx12527-28 at 613:12-614:22)).

The district court also relied on inventor testimony by Dr. Argaw Kidane explicitly linking the manufacturing protocol of Example 4 to

the homogeneous tablets that he and his co-inventors made prior to filing their application. (Appx132 (citing Appx12378 at 464:16–22)).

This Court has "made clear that the written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Ariad*, 598 F.3d at 1352. The inventors here, however, actually reduced to practice the claimed "homogeneous matrix" tablets described in their application the protocol used to make and test the tablets, and, during prosecution, explained to the Examiner that "formulations derived according to the protocol set forth in the Examples would necessarily comprise a homogeneous matrix." (Appx14089; Appx239-40, col.10 l.35-col.11 l.30). Evidence of the inventors' actual and constructive reductions to practice support the district court's written description findings. *Ariad*, 598 F.3d at 1352.

B. Supernus's Inventors Possessed Tablets that Remain Homogeneous Before, During, and After Hydration

The district court appropriately rejected Actavis's argument "that 'homogeneous matrix' in the specification described only the matrix-forming polymer once it was hydrated to the point of equilibrium, and

not the mixture of all four components in a 'homogeneous matrix' as ultimately claimed." (Appx131; Br. at 53).

First, during claim-construction proceedings below, Actavis expressly and unambiguously admitted that:

> The patents-in-suit **describe and claim** a specific type of formulation with a **'homogenous matrix' containing the active ingredient and excipients.**

(Appx548) (emphasis added). Actavis's post-trial argument that the patents only describe a hydrated matrix "and not the mixture of all four components in a 'homogeneous matrix'" directly contradicts this earlier admission. (Br. at 53).

Second, inventor Dr. Kidane testified that the matrix resulting from the disclosed manufacturing protocols remains homogeneous before, during, and after hydration because "the homogeneity does not change by the fact that these polymers swell." (Appx12379-80 at 465:1-466:5).

Third, the patent specifications confirm that the matrix produced by the disclosed manufacturing methods remains homogeneous before, during, and after hydration. (Appx237, col.5 ll.55-58 ("As the polymers

swell, **they form a homogenous matrix structure that maintains its shape during drug release** . . . .") (emphasis added)).

C. Actavis Waived Its "Breadth-of-the-Claims" Argument

Actavis argues that the district court's use of Example 4 to describe a homogeneous matrix allows Supernus to claim "any formulation which has that characteristic (a matrix in which all the ingredients are uniformly dispersed)." (Br. at 56). This new "breadth-of-the-claims" argument, however, was not presented at trial and therefore has been waived. *Fresenius USA, Inc. v. Baxter Int'l, Inc.*, 582 F.3d 1288, 1296 (Fed. Cir. 2009).

Even if it were not waived, Actavis's brief does not cite any evidence to support its "breadth-of-the-claims" contentions, relying solely on attorney argument. (Br. at 54, 56-57). Because Actavis has not presented any evidence, it cannot satisfy its clear-error burden. *See Gemtron Corp. v. Saint-Gobain Corp.*, 572 F.3d 1371, 1380 (Fed. Cir. 2009) ("unsworn attorney argument . . . is not evidence").

Actavis mistakenly relies on *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320 (Fed. Cir. 2000), to argue that Example 4 does not provide adequate written-description support for the "homogeneous

matrix" limitation. (Br. at 56-57). In *Purdue*, the patentee attempted to support a limitation requiring a "Cmax/C[24] ratio **greater than two**" by cherry-picking certain examples that disclosed data from which a ratio greater than two could be calculated. *Purdue*, 230 F.3d at 1326 (emphasis added). In finding that written description inadequate, this Court noted that "the specification also contains examples in which the Cmax/C[24] ratio is **less than two** and that nothing in the specification indicates to the skilled artisan **which examples embody the claimed invention and which do not**." *Id.* (emphasis added).

Here, every exemplified embodiment of Supernus's invention was created using the homogeneous-matrix technology disclosed in Example 4. (Appx239-40). The tables within Example 4 describe the precise composition—ingredient and amount—of all exemplified homogeneous tablets. (Appx239-40). And the detailed protocol describes how each of those exemplified homogeneous tablets were made. (Appx239-40). Unlike *Purdue*, the compositions and protocols of Example 4 can be understood and applied without the need to perform additional calculations or analyses. *Purdue*, 230 F.3d at 1326-27.

D. The District Court Did Not Conflate Written Description with Obviousness or Enablement

Among several attempts to recast findings of fact as legal error, Actavis argues that the district court conflated the obviousness and enablement standards with the written-description standard. (Br. at 57-61). It did not. The district court's written-description analysis is appropriately (and repeatedly) grounded in this Court's *Ariad* decision. (Appx130-31).

1. Written Description / Obviousness

With respect to obviousness, Actavis argues that "[t]he district court also erred in rejecting the written-description defense based on its finding that the working examples could comprise a homogeneous matrix or that it would be obvious for a formulator to make a homogeneous matrix based on the prior art." (Br. at 57-58). Actavis's paraphrase misstates the district court's finding. The district court actually stated, verbatim, that "Example 4 explicitly (not superficially) discloses the step by step manufacturing process **used by the inventors** to produce a homogeneous matrix tablet," not an obvious variation thereof. (Appx131-32) (emphasis added).

Actavis cites *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565 (Fed. Cir. 1997) and *Tronzo v Biomet, Inc.,* 156 F.3d 1154 (Fed. Cir. 1998), for the proposition that a disclosure that renders the claimed invention obvious is not necessarily sufficient to meet the written-description requirement. (Br. at 60). *Lockwood* and *Tronzo* have no bearing on this case because the district court found that "Example 4 explicitly (not superficially)" discloses the actual claimed homogeneous matrix tablets, not obvious variants thereof. (Appx131-32).

Actavis's expert testified that "the default objective for a pharmaceutical formulator would be to create a homogeneous matrix formulation." (Appx132-133 (citing Appx13406-07 at 1493:12-1494:4)). Actavis objects to the district court's reliance on this testimony in connection with its written-description analysis because, according to Actavis, its expert's "opinions regarding the obviousness of 'homogeneous matrix' is [sic] legally insufficient to prove written description." (Br. at 60). But again, the district court did not rely on this testimony to demonstrate that the specification discloses an obvious variant of the claimed invention. Rather, the district court relied on this testimony as confirmation that Supernus's inventors

possessed the claimed homogeneous tablets because: (i) "the default objective for a pharmaceutical formulator would be to create a homogeneous matrix formulation;" and (ii) Supernus's inventors used Example 4 to realize that default objective and reduce to practice the claimed homogeneous tablets. (Appx35-36; Appx132-34).

2. Written Description / Enablement

With respect to enablement, Actavis incorrectly argues that "[t]he district court also erred in rejecting Actavis's written-description defense based on its finding that the claims were enabled." (Br. at 60). As support for this argument, Actavis cites the district court's statement that "[t]he specification sets forth the manufacturing process in Example 4 [showing] how to produce a homogeneous matrix." (Appx133; Br. at 61).

Here again, the district court relied on Example 4 and other specification disclosures as evidence that Supernus's inventors actually made the claimed tablets, described the protocols used to make the tablets in their application, and disclosed analytical testing of the tablets made according to those protocols. Regardless of whether it is probative of enablement, such evidence confirms that Supernus's

patents satisfy the written-description requirement. *See Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 921 (Fed. Cir. 2004) (recognizing that while separate requirements, written description and enablement often have "significant overlap"); *see In re Edwards*, 568 F.2d 1349, 1352 (C.C.P.A. 1978) ("The description in the parent is not intrinsically defective *merely* because appellants chose to describe their claimed compound by the process of making it; our primary concern is whether the description requirement has been complied with, not the mode selected for compliance.").

The district court committed no clear error in finding that Supernus's inventors possessed the claimed homogeneous matrix formulations when they filed their applications.

IV. Definiteness: Skilled Artisans Understood with Reasonable Certainty the Scope of the Term "Homogeneous Matrix"

The district court applied the proper legal standard for definiteness—requiring that the "patent's claims, viewed in light of the specification and prosecution history, inform those skilled in the art about the scope of the invention with reasonable certainty." (Appx136-

37 (citing *Nautilus, Inc. v Biosig Instruments, Inc.,* 134 S. Ct. 2120, 2129 (2014))).

The district court correctly found—based on "persuasive[]" expert testimony (Appx138)—that "persons skilled in the art understood that 'homogeneous' means a mixture of two or more ingredients that are uniformly dispersed in a pharmaceutical formulation." (Appx137). Witnesses for both sides, including Actavis's experts and corporate representative, admitted that homogeneity may be assessed by: (i) a review of the process by which a tablet is manufactured; (ii) standard FDA uniformity testing; and/or (iii) chemical imaging.

Actavis fails to cite any expert opinion, learned treatise, or other proxy for a skilled artisan suggesting that a person of skill in the art would have difficulty understanding the scope of "homogeneous matrix" in the context of Supernus's claims.

A. The District Court's Definiteness Finding Is Supported by Fact and Expert Testimony, Including Testimony from Actavis's Own Experts

1. Skilled Artisans Assess the Manufacturing Process to Determine Tablet Homogeneity

The skilled artisan could have readily distinguished a homogeneous tablet from a non-homogeneous tablet based on the

process used to manufacture the tablet. Indeed, the district court expressly found that "Actavis's manufacturing process results in a homogeneous matrix in its tablets." (Appx40).

After walking the district court through each step of Actavis's manufacturing process—pre-mixing, chopping, blending, milling, and compression—Supernus's expert, Dr. Little, confirmed that "this process would produce a homogeneous matrix." (Appx21537; Appx12537 at 623:21-22). Relatedly, the district court credited Dr. Little's testimony:

> [W]hen one follows the manufacturing process as set forth in the examples in the Patents-in-Suit, as Supernus does to formulate Oxtellar XR® tablets, **a homogeneous matrix is necessarily achieved**.

(Appx31) (emphasis added). The district court was "persuaded by Dr. Little's expert opinion that if the constituents are properly blended, the final product will necessarily be uniform." (Appx42).

The district court further credited inventor testimony confirming that the manufacturing process will create (or not create) homogeneity: "the mixing that takes place during the manufacturing process of the Oxtellar XR® tablets creates homogeneity." (Appx31 (citing Appx12378-

79 at 464:16-465:25)). The district court found this testimony particularly credible in view of consistent statements made by the inventors during prosecution that "the formulations derived according to the [manufacturing] protocol set forth in the Examples would necessarily comprise a homogeneous matrix." (Appx39-40).

The district court also noted that "[e]ven Dr. Irwin Jacobs, Actavis's former expert that [Actavis] has since abandoned, characterized the Actavis ANDA product as 'a homogeneous matrix' **after reviewing Actavis's manufacturing process**." (Appx39-40 n.12) (emphasis added). Specifically, after reviewing "the details of [Actavis's] manufacturing process" (Appx12342 at 428:14-17)—but without having "seen all of the data as far as what Actavis has developed" (Appx12344 at 430:7-8)—Actavis's expert, Dr. Jacobs, characterized Actavis's Tablets as a "homogeneous matrix" platform. (Appx12343 at 429:11-22).

The district court also relied on Supernus's expert, Dr. Bugay, who "reviewed Actavis's manufacturing process as set forth in its ANDA" to "confirm[] his conclusion that the constituents are uniformly dispersed

in the Actavis Tablets such that the tablet comprises a homogeneous matrix." (Appx39).

Finally, Actavis's homogeneity expert, Dr. Muzzio, agreed that the manufacturing process (specifically, the blending steps) will dictate product homogeneity (or non-homogeneity). For example, on cross-examination, Dr. Muzzio admitted that "blend" means "to combine into a uniform mixture." (Appx12951-52 at1037:22-1038:3; Appx12953 at 1039:10-22; Appx5743-55 at Appx5746-48). Dr. Muzzio also admitted that "[b]lending is the homogenization of material by making all locations of the batch contain the same amount of all ingredients." (Appx12952 at 1038:5-11; Appx12955 at 1041:6-12).

In sum, both parties' experts and Supernus's inventors repeatedly acknowledged that one may discern a "homogeneous matrix" tablet from a "non-homogeneous matrix" tablet—i.e., discern the scope of the "homogeneous matrix" limitation with reasonable certainty—based on the manufacturing process.

2. Skilled Artisans Rely on FDA Uniformity and Dissolution Testing to Assess Tablet Homogeneity

The district court found that a person of ordinary skill in the art would turn to standardized FDA blend uniformity, content uniformity, and dissolution testing to demonstrate that a particular manufacturing process worked as intended (i.e., produced a homogeneous/uniform distribution of ingredients). (Appx40-46). The district court's finding, reviewed for clear error, was based on the consistent testimony of at least six pharmaceutical scientists (both parties' experts and fact witnesses).

Dr. Jacobs: Actavis's expert, Dr. Jacobs, testified that "there are a number of instrumental techniques to determine . . . what degree of homogeneity might be in [a] tablet," including testing of "the contents of the blender" (i.e., blend uniformity) and "tablet [] characteriz[ation]" (i.e., content uniformity). (Appx12345 at 431:9-12).

Dr. Little: The district court credited Supernus expert Dr. Little's testimony that blend uniformity "tests 'the adequacy of the mixing' by testing various samples from the blend to 'determine whether or not

[the] product is uniformly dispersed.'" (Appx41 (citing Appx12541 at 627:5-13)).

Although, as Actavis notes, blend uniformity directly measures only the active ingredient (here, oxcarbazepine), the district court was "persuaded by Dr. Little's expert opinion that if the constituents are properly blended, the final product will necessarily be uniform." (Appx42 (citing Appx12541 at 627:14-21)). Reiterating Dr. Little's testimony, the district court found that "[o]nce the uniformity of the active ingredient is established, a person of skill in the art would assume that all the other constituents of the blend are also uniformly dispersed." (Appx42 (citing Appx12544-45 at 630:16-631:4, Appx12643-45 at 729:21-731:1)).

The district court also credited Dr. Little in finding that "content uniformity testing also necessarily measures the quality of mixing in, as well as the homogeneity and uniformity of[,] the final tablet." (Appx43-44 (citing Appx12546 at 632:1-9)). The district court rejected Actavis's argument that content uniformity (which directly measures the distribution of a tablet's active ingredient) has no bearing on the homogeneity of the remaining ingredients:

> Dr. Little cogently explained that if the excipients were not uniformly dispersed, there would be localization of all constituents, including the active ingredient.

(Appx44).

Dr. Muzzio: The district court found that "Dr. Muzzio, Actavis's expert, agreed that a person of ordinary skill in the art generally assumes the uniform dispersion of the excipients once it has been established [through FDA blend uniformity testing] that the active ingredient is uniformly dispersed." (Appx42 n.13). Dr. Muzzio authored an article that states: "the [homogeneity] of a pharmaceutical blend is usually determined by assessing the uniformity of the active ingredient distribution throughout the mixture **while the uniformity of the excipients is assumed**." (Appx12969-70 at 1055:5-1056:5; Appx12971-73 at 1057:22-1059:20; Appx8305) (emphasis added). And reference texts favorably cited by Dr. Muzzio, such as the "Handbook of Pharmaceutical Granulation Technology," state that the properties of the blend "largely dictate the final product properties." (Appx12965-67 at 1051:12-1053:14).

The district court rejected Dr. Muzzio's opinion that content uniformity does not demonstrate tablet homogeneity because his

testimony on the subject contradicts his own recent publication, which acknowledges that "In-process dosage unit analysis [content uniformity]. . . is an accurate and reflective measure of homogeneity of the product." (Appx44 n.14 (citing Appx12963-65 at 1049:17-1051:6)).

Jack Chen: Actavis's Director of Analytical Chemistry, Jack Chen, testified as Actavis's Rule 30(b)(6) designee for homogeneity testing that "**a positive result or an in-specification result for blend uniformity would indicate that your product is homogeneous**." (Appx41; Appx12708 at 794:10-13) (emphasis added).

Dr. Kidane: Supernus inventor, Dr. Kidane, likewise testified that persons skilled in the art (including Supernus scientists) distinguish homogeneous tablets from non-homogeneous tablets using: (i) "blend uniformity" (Appx12375 at 461:12-17); (ii) "content uniformity" (Appx12376-77 at 462:18-463:3); and (iii) "dissolution profiles" (Appx12376 at 462:1-8).

Vitaliy Disman: Supernus analytical chemist, Vitaliy Disman, also testified that he relies on FDA uniformity and dissolution testing to confirm homogeneity. (Appx12356 at 442:13-19).

FDA Regulations: FDA's current good-manufacturing practices for finished pharmaceuticals (at 21 C.F.R. § 211.110) require companies to implement certain controls—including uniformity testing—to "**assure batch uniformity** and integrity of **drug products**." (Appx12539-40 at 626:5-6) (emphasis added). The FDA's guidance on uniformity testing likewise is "intended to assist manufacturers of human drug products in meeting the requirements of 21 C.F.R. § 211.110 for demonstrating the adequacy of mixing to **ensure uniformity of** in-process powder blends and **finished dosage units**." (Appx25117) (emphasis added).

The district court committed no clear error in relying on the consistent testimony of at least six pharmaceutical scientists to support its finding that a person skilled in the art would turn to FDA uniformity and dissolution testing to confirm that a product comprised a "homogeneous matrix" as claimed.

3. Skilled Artisans May Use Chemical Imaging to Confirm Tablet Homogeneity

The district court correctly found that "chemical imaging is a standard that confirms homogeneity, but it is not essential to the Patents-in-Suit to survive an indefiniteness challenge." (Appx138). In

other words, a person skilled in the art can determine whether a product satisfies the "homogeneous matrix" limitation without chemical imaging (e.g., by analyzing the manufacturing process and/or conducting standard uniformity or dissolution testing as explained above).

Further, the district court specifically rejected Actavis's argument that Dr. Bugay's chemical-imaging testimony "brought out" the "subjective and arbitrary nature" of the "homogeneous matrix" claim limitation:

> Actavis's protestations are actually borne out of its undue emphasis on chemical imaging and eschewal of the understanding of a homogeneous matrix by a person of ordinary skill in the art.

(Appx137; Br. at 63).

Actavis cites *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1350 (Fed. Cir. 2005) and *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 760-61, n.2 (2011), for the proposition that "the boundaries of the claims could not turn on the intent of the purported infringer or his or her subjective preferences." (Br. at 66-67). Both cases are inapposite because neither Supernus nor the district court argued that the scope of "homogeneous matrix" depends on the intent of

the pharmaceutical manufacturer. Rather, as the district court found, a person of ordinary skill understands a tablet to be homogeneous (and infringing) if the manufacturing process provides sufficient mixing to uniformly disperse all ingredients, which can readily be confirmed by FDA uniformity testing or chemical imaging. (Appx40-61; Appx137-38).

Actavis also cites to *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1218 (Fed. Cir. 1991), to argue that "homogeneous matrix" is indefinite because the district court found, based on Dr. Muzzio's admission, that "there are degrees of homogeneity." (Br. at 67; Appx60 (citing Appx12818 at 904:11)). Actavis argues that, because some tablets may be more or less uniform than others, an "objective standard" is required to ascertain what degree of homogeneity is covered by the claims. (Br. at 67). Actavis's argument misses the point.

The claims require a "homogeneous matrix," which the district court defined as "a matrix in which the ingredients or constituents are uniformly dispersed." (Appx20). So long as the ingredients are uniformly dispersed, they constitute a "homogeneous matrix," regardless of the degree of uniformity achieved. *Shamrock Techs., Inc. v. Med. Sterilization, Inc.*, 903 F.2d 789, 792 (Fed. Cir. 1990) (noting

that "[i]nefficient infringement is infringement still" and rejecting defendant's argument that the accused product was not "uniformly irradiated" merely because they did "not achieve perfect uniformity").

Indeed, the district court explicitly noted that, "[t]hroughout the trial, it was evident that persons skilled in the art understood that homogeneity varied in degrees." (Appx137).

Finally, Actavis cites to *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364 (Fed. Cir. 2014), for the proposition that "homogeneous matrix" is indefinite because the manufacturing process disclosed in Example 4 "provides no standard by which to judge whether the ingredients in any given formulation are or are not 'uniformly dispersed.'" (Br. at 68). In *Interval Licensing*, this Court found the limitation "in an unobtrusive manner that does not distract the user" indefinite because: (i) the "'unobtrusive manner' phrase is highly subjective and, on its face, provides little guidance to one of skill in the art;" and (ii) the intrinsic record "reflect[s] considerable uncertainty about which embodiments were tied to the 'unobtrusive manner' language." *Interval Licensing*, 766 F.3d at 1371-72.

Here, in contrast, the district court found that: (i) "homogeneous matrix" is not subjective because "[i]t is clear that persons skilled in the art understood that 'homogeneous' means a mixture of two or more ingredients that are uniformly dispersed;" and (ii) the specification clearly states that all embodiments of the claimed formulations were made according to the process disclosed in Example 4. (Appx137-38). Moreover, unlike "unobtrusive manner," a skilled artisan can confirm homogeneity using standard industry tests. (Appx40-61; Appx137-38). *Interval Licensing* explicitly recognized that "[c]laim language employing terms of degree has long been found definite" where, as with Supernus's patents, the specification "provide[s] enough certainty to one of skill in the art when read in the context of the invention." *Interval Licensing*, 766 F.3d at 1370.

Supernus's Dr. Little testified that "homogeneous matrix" is "not indefinite," and explained in detail how the manufacturing process and uniformity testing can confirm homogeneity. (Appx13545 at 1632:9-10; Appx13580 at 1667:2-16). Actavis elected not to cross examine Dr. Little on definiteness or provide competing expert testimony. Supernus's Dr. Bugay additionally testified at length regarding how a

person of ordinary skill can use chemical imaging to confirm homogeneity. (Appx12287 at 373:3-22; *see generally* Appx12244-63; Appx12233-40). The district court found Dr. Bugay's explanation so cogent and persuasive, that it "merit[ed] reproduction [in its opinion] in full." (Appx52-53 (citing Appx12287 at 373:3-22)).

Actavis's brief, on the other hand, cites no expert opinion supporting the proposition that a person of skill in the art would not understand the scope of "homogeneous matrix." Without expert testimony, Actavis cannot prove indefiniteness by clear and convincing evidence. *See Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1068 (Fed. Cir. 2005) ("Unsubstantiated attorney argument regarding the meaning of technical evidence is no substitute for competent, substantiated expert testimony."); *Elcommerce.com, Inc. v. SAP AG*, 745 F.3d 490, 506 (Fed. Cir. 2014) *vacated on other grounds by* 564 Fed. App'x 599 (Fed. Cir. 2014) (holding that the burden to prove indefiniteness was on the accused infringer, "and in the absence of evidence provided by technical experts who meet the *Daubert* criteria there is a failure of proof").

The district court committed no error in determining that a POSA could reasonably ascertain the scope of homogeneous matrix.

CONCLUSION

For at least the reasons expressed above, this Court should affirm the district court's judgment in all respects.

Dated: July 8, 2016

Respectfully submitted,

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PROOF OF SERVICE

I hereby certify that on July 8, 2016, the foregoing "NON-CONFIDENTIAL BRIEF FOR PLAINTIFF-APPELLEE" was served electronically on counsel of record.

/s/ Nicholas F. Giove

CERTIFICATE OF COMPLIANCE WITH FED. R. APP. P. 32(a)(7)(B)

I hereby certify that the foregoing "NON-CONFIDENTIAL BRIEF FOR PLAINTIFF-APPELLEE" complies with the type-volume limitation in Rule 32(a)(7)(B) of the Federal Rules of Appellate Procedure. In particular, it contains 13,738 words as reported by the word-processing program Microsoft® Word® 2010 in 14 point type size with Century Schoolbook font.

Dated: July 8, 2016 /s/ Nicholas F. Giove